

Influence of Body Mass Indexes on Response to Treatment in Acute Asthma

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Abstract- Increases in body mass index (BMI) are reported to influence asthma response to treatment. The aim of this study was to investigate the relationship between BMI and response to treatment in a group of patients that were referred for asthma control. Effectiveness measurements in this analysis included percentage of changes in forced volume in 1 second (FEV1), forced volume capacity (FVC), FEV1/FVC, and forced expiratory flow between 25% and 75% of FVC (FEF25–75%). A total of 293 subjects with asthma of both genders and above 18 years of age were divided into the following BMI categories: 107 (36.5%) non-obese (BMI <25), 186 (63.5%) overweight and obese (BMI ≥25). Percentage of change was defined as change in variable between baseline and end-of-treatment. Analyses of non-obese vs. overweight/obese asthmatics demonstrated non-significant differences in baseline FEV1 (1.62±0.56 Lit vs. 1.63±0.56 Lit L, $P=0.89$); FVC (2.58±0.73 Lit vs. 2.47±0.82 Lit, $P=0.25$); and FEF25-75% (1.04±0.55 ml/sec vs. 1.05±0.50 ml/sec, $P=0.47$) respectively. Compared with non-obese subjects, in overweight/obese subjects with asthma were less responded to treatment. Percentage changes of FEV1, FVC, FEF25-75%, and FEV1/FVC in non-obese versus obese/overweight patients were: 79.57±55.14 % vs. 62.13±41.72%, $P=0.005$; 47.71±33.76% vs. 39.93±28.30%, $P=0.036$; 151.98±127.82% vs. 123±91.12%, $P=0.041$; 20.54±15.63% vs. 15.63±11.32%, $P=0.005$; respectively. Percentage changes of spirometric values to treatment in over weight/obese asthmatic patient were lesser in compared with non-obese subjects.

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Introduction

Asthma and obesity are major public health problem, which have been rapidly increasing in prevalence in the world (1,2). The literature suggests that there is an association between obesity and asthma. Most prospective studies show that obesity is a risk factor for the de novo diagnosis of asthma, with the risk increasing between 1.1-fold and 3-fold (3-5). Obesity is associated with a poor response to conventional asthma therapies.

Previous studies have indicated that obese subjects with asthma report greater morbidity, greater resistance to therapy, and poorer asthma control than normal-weight subjects with asthma (6-8). Overweight and obesity are associated with glucocorticoid responsiveness and with an inability to achieve adequate asthma control both with inhaled corticosteroids and combination therapies that include inhaled corticosteroids and long acting bronchodilators (9-12). In a study that was conducted by Camargo *et al.*, compared to subjects with normal BMI,

the onset to peak FEV1 may require longer treatment exposure in the very obese asthmatic patients (13). Multiple studies have found a blunted response to corticosteroids in overweight and obese asthmatics. In a study Peters-Golden *et al.*, demonstrated that the response to inhaled corticosteroids inversely correlated with increasing BMI (14). In another study that was performed in moderate asthmatic patients, obese patients were less likely than non-obese patients to achieve asthma control with either fluticasone or fluticasone/salmeterol (9). In a study that was conducted by Forno *et al.*, overweight and obese children had less response to budesonide compared to non-overweight children (15).

The purpose of this study was to determine the effect of obesity on response to treatment in acute asthmatic patients.

Materials and Methods

The study was carried out on adult patients in a

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private clinic treated for acute asthma, between March 2007 and February 2009, with a 2 week period follow-up. All patients were treated with an inhalation of Short-acting beta2-agonist use for symptom control, with high dose Fluticasone / salmeterol (250 µg-50 µg) 2 inhalation twice daily, and a short course of oral prednisone (40 -60 mg daily). After two weeks, a new spirometric assessment was performed under the same conditions in all patients.

Non-obese was defined as BMI < 25 kg/m², and overweight/obesity was defined as BMI ≥ 25 kg/m². The body-mass index (BMI) is calculated by dividing weight (in kg) by the square of height (in meters). Height and weight were measured in light clothing without shoes for calculation of BMI in kilograms per square meter. Spirometry was measured at baseline and 2 weeks after the treatment, by using a spirometer (Fukuda, ST-95; Fukuda Sangyo Inc., Antipolo City, The Philippines). At least three acceptable maneuvers meeting American Thoracic Society (ATS) standards were required, with at least two reproducible forced expiratory volumes in 1 second (FEV1) and forced vital capacity (FVC) maneuvers within 5% of best required for each test. The treatment was adjusted for each patient according to the severity of the disease. All patients had age 18 and over, were symptomatic and had uncontrolled asthma using a short acting beta agonist alone.

The primary outcome measure was percentage change in pretreatment FEV1 from baseline to the end of each of the treatment periods. The subjects included adult asthmatic patients with a FEV1 < 80% predicted, which were recruited from out-patients referred to office for treatment. Only individuals who had completed the treatment period were included in the study. The diagnosis of asthma was made on clinical grounds and

required objective criteria of reversible airway obstruction as [an improvement in FEV1 ≥ 12% (and ≥ 200 ml) after inhalation of a short-acting β₂-agonist] defined by the American Thoracic Society (16). Informed consent was obtained from all the participants before the studies were carried out.

The results of pulmonary function tests were calculated as a percentage of change relative to baseline spirometric values using the following equation:

Percentage of change = [(observed – base) / base] × 100, where observed is the post treatment values, base is the baseline value on the day before the treatment.

Data are expressed as mean ± SD. The Kolmogorov-Smirnov test was used for the distribution of quantitative variables. Mean ± SD values of pulmonary function tests (FEV1, FVC, FEF25-75% and FEV1/FVC) prior to and after the treatment were calculated, and p values were compared by means of Student's t-test for paired and unpaired data. Comparisons between the groups were evaluated using the Mann-Whitney U-test or the Wilcoxon signed-rank test, when appropriate. Values of p < 0.05 were considered significant. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Result

Two hundred ninety-three patients (mean, 41.35 years; 53.9% male) with acute asthma (FEV1, 52.03% of predicted) were enrolled in the study. On the basis of determined criteria, 186 patients (63.5%) were classified as overweight/obese (BMI ≥ 25 kg/m²).

Comparisons of different variables stratified by BMI are shown in Table 1.

Table 1. Baseline demographics and spirometric characteristics by body mass index category*

Variable	BMI < 25 kg/m ² (n=107)	BMI ≥ 25 kg/m ² (n=186)	p Value
Age, yrs	39.50±14.25	42.41±14.19	0.09
Male/Female	71/36	87/99	-
baseline FEV1, lit	1.62±0.56	1.63±0.56	0.89
baseline FEV1, %pred.	49±13.67	53.77±12.84	0.003
Baseline FVC, lit	2.58±0.73	2.47±0.82	0.25
Baseline FVC, %pred.	65.74±14.43	68.07±14.03	0.18
Baseline FEF25- 75%, l/sec	1.04±0.55	1.05±0.47	0.85
Baseline FEF25-75%, %pred.	25.02±11.37	28.05±12.01	0.04
BMI	22.05±2.19	30.15±3.91	<0.001
Baseline FEV1/FVC%	62.45±9.61	66.09±8.19	0.09

*Data are presented as mean±SD. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF25-75%: forced expiratory flow between 25% and 75% of FVC

Analyses of non-obese versus overweight/obese asthmatic subjects demonstrated no significant differences in baseline FEV1 (1.62±0.56 L vs 1.63±0.56 L, P=0.89), FVC (2.58±0.73 L vs 2.47±0.82 L, P=0.25), FEF 25-75% (1.04±0.55 l/sec vs 1.05±0.47 l/sec; P=0.85). Obese subjects had a mean of BMI 30.15±3.91 while in non-obese subjects, it was 22.05±2.19 (p<0.001). In the overweight/obese subjects with asthma group, the BMI range was 25 to 43.28 kg/m2.

Overweight/obese asthmatic patients were slightly older, and more likely to be female than non-obese patients. Overall, in overweight/obese subjects with asthma, women had a significantly higher BMI than men

(31.18±4.23 kg/m2 vs 29±3.15 kg/m2, p<0.001). As compared to non-obese asthmatics, a slight increase in FEV1/FVC was observed in overweight/obese asthmatics (66.09±8.19 vs 62.45±9.61; P=0.09).

Table 2, summarizes the results of FEV1, FVC, FEF25-75%, and FEV1/FVC in both groups of non-obese and overweight/obese acute asthmatic patients. As shown in Table 2, there were significant differences between the mean pre-treatment and post-treatment values of FEV1, FVC, FEF25-75% and FEV1/FVC (P<0.001 for all).

Table 2. Comparison of pulmonary function variables between non-obese and those with overweight/obese asthmatic patients*

Variable	BMI<25 kg/m2(n=107)				BMI≥25 kg/m2(n=186)			
	Pre treatment	post treatment	95%CI	P value	Pre treatment	Post treatment	95%CI	p value
FEV1,lit	1.62±0.56	2.76±0.83	-1.26 -1.02	<0.001	1.63±0.56	2.53±0.70	-0.96 -0.83	<0.001
FEV1,pred.	49.15±13.67	82.94±16.61	-37.06 -30.83	<0.001	53.77±12.84	83.72±14.18	-31.94 -27.96	<0.001
FVC,lit	2.58±0.73	3.68±0.89	-1.22 -0.98	<0.001	2.47±0.82	3.34±0.91	-0.94 -0.79	<0.001
FVC,pred.	65.74±14.43	93.18±13.28	-30.25 -24.63	<0.001	68.07±14.03	92.68±13.20	-26.62 -22.61	<0.001
FEF25-75%,litsec	1.04±0.55	2.37±1.25	-1.54 -1.12	<0.001	1.05±0.47	2.16±0.91	-1.21 -1.01	<0.001
FEF25-75%,pred.	25.02±11.37	58.46±25.49	-38.20 -28.67	<0.001	28.05±12.01	58.42±22.05	-32.96 -27.78	<0.001
FEV1/FVC	62.45±9.61	74.47±9.92	-13.65 -10.38	<0.001	66.09±8.19	75.80±6.95	-10.64 -8.78	<0.001

*Data are presented as mean±SD. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF25-75%: forced expiratory flow between 25% and 75% of FVC

In Table 3, comparison of percentage changes of spirometric variables between non-obese and those with overweight/obese asthmatic patients are summarized.

Percentage changes of FEV1, FVC, FEF25-75%, and FEV1/FVC in both groups of obese/overweight and non-obese subjects are statistically significant.

Table 3. Comparison of percentage changes of spirometric variables between nonobese and those with overweight/obese asthmatic patients

Variable	BMI<25 kg/m2 (n=107)	BMI≥25 kg/m2 (n=186)	95%CI	p Value
FEV1 change	79.57±55.14	62.13±41.72	5.32-29.58	0.005
FVC change	47.71±33.76	39.93±28.30	0.52-15.04	0.036
FEF25-75% change	151.98±127.82	123±91.12	1.25-56.71	0.041
FEV1/FVC change	20.54±15.63	15.63±11.32	1.51-8.31	0.005

*Data are presented as mean±SD. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF25-75%: forced expiratory flow between 25% and 75% of FVC

Discussion

This study demonstrates that compared with non-overweight asthmatic patients, response to therapy in overweight/obese subjects showed a decreased on measures of spirometric values. In this study percentage change of FEV1, FVC, FEF25-75% and FEV1/FVC in two groups of patients is 0.005, 0.036, 0.041 and 0.005; respectively.

Previous studies have examined the relationship between BMI and response of treatment in acute asthma patients. In a study that was conducted by Carroll *et al.*, on 209 children admitted to the ICU with status

asthmaticus, they found that obese children had a significantly longer ICU and hospital length of stay (17). Rodrigo *et al.*, reported that overweight/obese patients were admitted to the hospital more frequently than underweight/normal patients (18).

In the current study percentage changes of FEV1 in both groups of obese and non-obese subjects are 79.57±55.14 and 62.13±41.72; respectively (P=0.005). In a study that was conducted by Rodrigo *et al.*, percentage changes of FEV1 in two groups of patients with BMI<25 with those of BMI ≥ 25 were 108.8±94.4% and 95.0±80.1%; P=0.12 (18). Unlike our study, they measured percentage changes of FEV1 and

peak expiratory flow rate immediately before starting treatment and at 30-min intervals until discharge or hospital admission, within the first 6 h after presentation. In another study Lessard *et al.*, concluded that obese people with asthma had poorer asthma control than non-obese asthmatics despite similar bronchodilator response (19). In their study post bronchodilator measurements were made 15 minutes after the administration of 200 µg of inhaled salbutamol (19).

In a study Tantisira *et al.*, noted an inverse relationship between BMI and bronchodilator response (20). In their study while BMI was positively associated with the methacholine concentration that causes a 20% fall in forced expiratory volume in 1 second, however, decrements in the FEV1/FVC ratio were noted with increasing BMI. Taylor *et al.*, determined that obesity is associated with increased daily asthma symptoms, missed workdays, increased rescue bronchodilator usage and increased asthma severity as determined by GINA guidelines (6).

Concurrent with more severe disease is a poor response to conventional asthma therapies. According to data from Lavoie *et al.*, asthmatics with higher BMI have worse asthma control (assessed by the Asthma Control Questionnaire) and lower Asthma Quality of Life Questionnaires, regardless of disease severity (21). It is difficult to determine the potential mechanisms responsible for the relationship between overweight/obesity and decreased response to therapy. Potential mechanisms include obesity-related changes in lung volumes, systemic inflammation, and other adipocyte-derived factors that might alter airway smooth muscle function in such way as to promote airway narrowing (22,23).

The mechanisms that mediate the differential treatment response to corticosteroids are unknown. One potential mechanism by which this could be hypothesized to occur is altered molecular response to GCs due to systemic inflammation. GCs inhibit proinflammatory gene expression, in part through negative regulation of mitogen-activated protein kinase (MAPK) signaling pathways by molecules such as MAPK phosphatase (MKP)-1 (24). Given that proinflammatory cytokines, such as IL-1, IL-6, and TNF- α , are increased in many obese individuals, and given that these same cytokines are regulated by and potential regulators of p38 MAPK (24), it is possible that this proinflammatory environment might modify GC function in obese patients with asthma. They hypothesized that overweight and obese patients with asthma would demonstrate evidence of reduced

molecular responsiveness to GCs (manifested by reduced induction of MKP-1 expression in response to GC treatment *in vitro*) in immune cells derived from both the peripheral blood and lung, a process potentially mediated by enhanced expression of or sensitivity to TNF- α .

Sutherland *et al.*, proposed decreased mitogen-activated protein kinase phosphatase-1 (MKP-1) expression in peripheral blood mononuclear cells (PBMCs) and lung cells likely macrophages (12). Other postulated mechanisms for the variable response to therapy include the assertion that obesity has effects on asthma control mediated by obesity related changes in lung mechanics (25). Additional proposed mechanisms include the potential role of vitamin D deficiency on glucocorticoid responsiveness. Vitamin D deficiency is more common in obese individuals as demonstrated by Sutherland *et al.*, who found an inverse relationship between vitamin D levels and BMI (26). More importantly, low vitamin D levels are associated with decreased glucocorticoid responsiveness in asthma (28).

This study demonstrates, percentage changes of FEV1, FVC, FEF25-75%, and FEV1/FVC to treatment in over weight/obese asthmatic patient were lesser in compared with non-overweight subjects, and is statistically significant.

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